# Meningococcus Meningitis

## *Three Cases Resistant to Penicillin*

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PENICILLIN IS WELL-KNOWN as the antibiotic of choice in the treatment of Neisseria meningitidis infection. Also of great interest is the extraordinary sensitivity of this organism to the sulfonamides. In the Glasgow epidemic of 1907 there was a case fatality rate of 70 per cent. From 1920 to 1936, the composite case fatality rate as computed from reports in various areas of the United States was 51.2 per cent. This was after the advent of the use of immune serum in the treatment of the disease.

Penicillin and the sulfonamides have strikingly lowered the fatality rates of meningococcal meningitis to less than 10 per cent. Some physicians feel that the use of two antibiotics may be harmful, but in the three cases reported upon herein, two antibiotics were used until it was found that the organisms were resistant to penicillin, and there were no harmful effects clinically evident. Two of the patients had been given penicillin at various times previously, and in them the organisms were completely resistant to penicillin.

CASE 1. An 18-year-old white male was admitted to hospital the night of Jan. 31, 1953, with a history of vomiting, then sore throat and fever (103° F.) for 24 hours and a slight headache and extreme restlessness the night before admittance. The morning of the day of admittance, the patient noted a rash on his body. He had had "flu," consisting of sore throat and nausea, a week before. Intermittently during the previous year he had received penicillin for sore throat and colds.

Upon physical examination the patient was observed to be lying quietly in bed, alert and complaining of headache. There were petechiae scattered over the trunk and extremities as well as in the conjunctivae. The vessels of the throat were engorged. There was pain on flexion of the neck, but no nuchal rigidity. Deep tendon reflexes were normal and no pathological reflexes were noted.

The spinal fluid was cloudy and contained Gram-negative diplococci. A diagnosis of meningococcic meningitis was made. Neisseria meningitidis grew on cultures of spinal fluid and blood, Streptococcus viridans and Staphylococcus aureus on cultures of material from the throat, and Staphylococcus albus and diphtheroids on cultures of exudate from petechiae.

Therapy consisted of five million units of sodium penicillin intravenously and twenty-five million units of potassium penicillin every eight hours for five days until sensitivity studies were returned. The organisms were reported resistant to penicillin; moderately sensitive to streptomycin; and highly sensitive to chloramphenicol and Terramycin. The patient had allergic sensitivity to sulfa drugs, so none was given. At first 500 mg. of chloromycetin was given intravenously every two hours, four times; then intramuscularly every three hours until Feb. 3, and then 500 mg. orally every four hours.

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**TABLE 1.—*Data on cerebrospinal fluid and blood (Case 1)***

CEREBROSPINAL FLUID

| Date | Cells: Total per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Sugar* | Pandy Test reaction |
|---|---|---|---|---|---|
| Jan. 31, 1953 | 450 | 100 | .... | 5 gtt. | 1 plus |
| Feb. 1, 1953 | 4,180 | 98 | .... | 3 gtt. | 3 plus |
| Feb. 2, 1953 | 1,126 | 75 | 25 | 3 gtt. | 2 plus |
| Feb. 3, 1953 | 716 | 70 | 30 | 4 gtt. | 1 plus |
| Feb. 4, 1953 | 75 | 55 | 20 | 4 gtt. | trace |
| Feb. 5, 1953 | 40 | 6 | 34 | 2 gtt. | trace |
| Feb. 6, 1953 | 32 | 3 | 29 | 3 gtt. | trace |
| Feb. 9, 1953 | 8 | .... | 100 | trace | trace |
| Feb. 12, 1953 | 11 | .... | 100 | 3 gtt. | trace |
| Feb. 15, 1953 | 11 | .... | 100 | 5 gtt. | trace |
| Feb. 18, 1953 | 4 | .... | 100 | 3 gtt. | trace |
| Feb. 21, 1953 | 5 | .... | 100 | 3 gtt. | trace |

*Stated in number of drops of spinal fluid required to reduce 1 cc. of Benedict's solution (normal, 2 to 3 drops).

BLOOD

| Date | Cells: Leukocytes per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Hemoglobin (gm.) |
|---|---|---|---|---|
| Jan. 31, 1953 | 42,000 | 92 | .... | 13.5 |
| Feb. 1, 1953 | 30,000 | 95 | .... | 13.5 |
| Feb. 3, 1953 | 13,600 | 84 | 16 | 12.5 |
| Feb. 4, 1953 | 8,400 | 77 | 23 | 15.0 |
| Feb. 5, 1953 | 19,700 | 80 | 20 | 13.5 |
| Feb. 14 1953 | 10,550 | 48 | 52 | 13.0 |
| Feb. 17, 1953 | 19,400 | 74 | 26 | 15.5 |
| Feb. 20, 1953 | 9,100 | 71 | 29 | 12.5 |

The clinical course was satisfactory and on Feb. 4 the patient was tolerating diet well. He became afebrile on Feb. 7 and remained so. Data on laboratory examinations of the cerebrospinal fluid and the blood are given in Table 1.

Electroencephalograms on various dates were as follows: Feb. 1, moderately diffuse, abnormal; Feb. 9, normal; Feb. 11, moderately diffuse, abnormal; Feb. 16, mildly diffuse, abnormal; Feb. 20, normal.

Antibiotic therapy was discontinued Feb. 15 and the patient was discharged Feb. 22, twenty-two days after admission, free of symptoms.

CASE 2. A two-year-old white girl was admitted to hospital Feb. 3, 1953, with history of fever (102° F.), listlessness and malaise of five days' duration. The night symptoms started, the patient had a convulsion that lasted more than five minutes and she vomited anything ingested. The next day a physician examined her and administered 600,000 units of penicillin. She continued listless and febrile but did retain some liquids. The following day penicillin was administered again, and then 300,000 units every six hours.

The day before admission to hospital the patient had pain in the knees and elbows but there were no more convulsions or vomiting. Nuchal rigidity developed, however, and the patient was hospitalized. Until the present illness she had never been given penicillin.

When examined upon admittance, the patient was lethargic, listless and very irritable. There were no petechiae present on the body. The vessels of the nose were engorged but the pharynx was clear. There

**TABLE 2.—*Data on cerebrospinal fluid and blood (Case 2)***

CEREBROSPINAL FLUID

| Date | Cells: Total per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Sugar | Pandy Test reaction |
|---|---|---|---|---|---|
| Feb. 3, 1953 | 1,296 | 64 | 36 | 7 gtt. | 2 plus |
| Feb. 4, 1953 | 504 | 74 | 26 | 3 gtt. | 1 plus |
| Feb. 5, 1953 | 522 | 62 | 38 | 3 gtt. | trace |
| Feb. 6, 1953 | 132 | 84 | 16 | 3 gtt. | 2 plus |
| Feb. 7, 1953 | 58 | 3 | 55 | 3 gtt. | ..... |
| Feb. 10, 1953 | Bloody | .... | .... | ..... | ..... |
| Feb. 13, 1953 | 12 | 1 | 11 | 3 gtt. | trace |
| Feb. 17, 1953 | 11 | 1 | 10 | 3 gtt. | slight trace |
| Feb. 20, 1953 | 18 | .... | 18 | 3 gtt. | trace |
| Feb. 23, 1953 | Bloody | .... | .... | ..... | ..... |
| Feb. 26, 1953 | Bloody | .... | .... | ..... | ..... |
| Mar. 1, 1953 | ..... | .... | 1 | 3 gtt. | trace |
| Mar. 3, 1953 | Bloody | 4 | 29 | ..... | ..... |
| Mar. 9, 1953 | 22 | 2 | 20 | ..... | trace |
| Mar. 13, 1953 | 6 | .... | all | 3 gtt. | neg. |

BLOOD

| Date | Leukocytes per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Hemoglobin (gm.) |
|---|---|---|---|---|
| Feb. 3, 1953 | 27,000 | 91 | 9 | 12.0 |
| Feb. 4, 1953 | 16,500 | 58 | 42 | 12.5 |
| Feb. 5, 1953 | 18,950 | .... | .... | ..... |
| Feb. 6, 1953 | 9,000 | 42 | 58 | 10.0 |
| Feb. 8, 1953 | 7,000 | 80 | 20 | 12.0 |
| Feb. 14, 1953 | 10,200 | 52 | 48 | 11.0 |
| Feb. 17, 1953 | 7,200 | 62 | 38 | 13.0 |
| Feb. 20, 1953 | 9,950 | 56 | 44 | 12.0 |
| Feb. 26, 1953 | 5,200 | 62 | 38 | 15.0 |
| Mar. 1, 1953 | 7,400 | 38 | 62 | 12.0 |
| Mar. 9, 1953 | 7,600 | 50 | 50 | 12.5 |
| Mar. 12, 1953 | 6,000 | 50 | 50 | 13.0 |

was three plus nuchal rigidity and the Kernig and Brudzinski signs were present. Spasm of two plus degree was noted in the back and hamstring muscles. Deep tendon reflexes were equal and hyperactive.

A specimen of spinal fluid was grossly cloudy and Gram-negative diplococci were observed on microscopic examination. Neisseria meningitidis grew on cultures of spinal fluid but there was no growth on cultures of the blood. Cultures of material from the throat produced Staphylococcus albus.

The patient received 200 million units of potassium penicillin in the first 72 hours in the hospital. Terramycin was given intravenously, 250 mg. every four hours for two days and then 250 mg. every six hours for one day. Then Terramycin was given by mouth, 250 mg. every four hours for two days and then that amount every six hours. Terramycin then was discontinued and sodium penicillin (1 million units) was given every four hours for two days, as well as penicillin, 600,000 units twice daily for five days. In vitro, the organism was resistant to low concentrations of penicillin and moderately sensitive to high concentrations. They were resistant to streptomycin and highly sensitive to chloramphenicol, aureomycin and Terramycin. The patient was given 1.75 gm. each of sulfadiazine and sulfisomidine on admission but this medication was discontinued because of erythrocytes in the urine.

**TABLE 3.—*(Case 3) Data on cerebrospinal fluid and blood, and on concentrations of sulfa drugs administered***

CEREBROSPINAL FLUID

| Date | Cells: Total per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Sugar | Pandy Test reaction |
|---|---|---|---|---|---|
| Feb. 8, 1953 | 42 | 88 | 12 | 4 gtt. | neg. |
| Feb. 9, 1953 | 853 | 81 | 19 | 2 gtt. | trace |
| Feb. 11, 1953 | 135 | 62 | 38 | 2 gtt. | trace |
| Feb. 12, 1953 | 30 | 6 | 24 | 3 gtt. | trace |
| Feb. 14, 1953 | 1 | .... | 1 | 3 gtt. | trace |
| Feb. 16, 1953 | 0 | .... | .... | 3 gtt. | trace |
| Feb. 17, 1953 | 11 | .... | 11 | 3 gtt. | trace |
| Feb. 20, 1953 | Bloody | .... | .... | ..... | ..... |
| Feb. 23, 1953 | 8 | .... | 8 | 3 gtt. | 1 plus |
| Feb. 26, 1953 | 4 | 1 | 3 | 3 gtt. | trace |
| Mar. 1, 1953 | 9 | 3 | 6 | 3 gtt. | 1 plus |
| Mar. 6, 1953 | 5 | 2 | 3 | 3 gtt. | ..... |

BLOOD

| Date | Leukocytes per cu. mm. | Cells: Polymorphonuclear (Pct.) | Cells: Lymphocytes (Pct.) | Hemoglobin (gm.) |
|---|---|---|---|---|
| Feb. 8, 1953 | 10,100 | 70 | 30 | 15.0 |
| Feb. 9, 1953 | 23,200 | 55 | 45 | 12.5 |
| Feb. 10, 1953 | 19,000 | 85 | 15 | 10.5 |
| Feb. 11, 1953 | 16,600 | 80 | 20 | 12.5 |
| Feb. 12, 1953 | 9,650 | 75 | 25 | 11.0 |
| Feb. 14, 1953 | 6,400 | 46 | 54 | 13.0 |
| Feb. 16, 1953 | 8,450 | 55 | 45 | 14.0 |
| Feb. 17, 1953 | 9,250 | 73 | 27 | 13.0 |
| Feb. 20, 1953 | 9,450 | 53 | 47 | 12.5 |
| Feb. 26, 1953 | 5,600 | 62 | 38 | 15.0 |
| Mar. 1, 1953 | 9,000 | 48 | 52 | 13.0 |
| Mar. 6, 1953 | 7,450 | 67 | 33 | 13.0 |

SULFA DRUG CONCENTRATIONS (mg. per 100 cc.)

| Date | Blood | Spinal fluid | Urine | pH of urine |
|---|---|---|---|---|
| Feb. 9, 1953 | 25.0 | 11.1 | 7.9 | 6.0 |
| Feb. 10, 1953 | 49.2 | 31.2 | ..... | .... |
| Feb. 11, 1953 | 40.6 | 25.0 | 34.3 | 5.0 |
| Feb. 12, 1953 | 62.5 | 37.5 | 87.5 | 5.0 |
| Feb. 14, 1953 | 9.3 | 5.0 | 10.0 | .... |
| Feb. 16, 1953 | 1.2 | 1.2 | 5.3 | .... |
| Feb. 17, 1953 | 0 | 0 | 0 | .... |

The clinical course was satisfactory and the day following admission the patient was ingesting fluids. No convulsions occurred. The temperature was 101° F. on admission and varied from 98.2 to 100.4° F. until Feb. 10. Thereafter the temperature rose occasionally to 100.2° F. up to the time of discharge from the hospital.

Data on laboratory examination of the spinal fluid and blood are given in Table 2.

Antibiotic therapy was stopped on March 1 and the patient was discharged as cured 39 days after admission to the hospital.

CASE 3. A four-and-one-half-year-old white boy was admitted to hospital Feb. 8, 1953, with two-day history of rhinitis and pain in the legs and feet and of vomiting and fever for one day. The patient had been well previously except for "runny nose." The evening he entered the hospital the patient's mother noted a rash on his abdomen, which spread over the body. There was no history of exposure to any disease. The patient previously had had penicillin from time to time for frequent colds and sore throat.

Upon physical examination the patient was observed to be acutely and severely ill, but apprehensive and oriented. The temperature was 104.6° F. and the blood pressure 102/60 mm. of mercury. Generalized petechial eruption was present over the trunk and extremities. The face was flushed. There was one plus nuchal rigidity. Reflexes were equal and active. Kernig's sign was present. The spinal fluid was clear.

A diagnosis of meningococcus meningitis was made and treatment was started. Cultures of spinal fluid and petechial exudate grew Neisseria meningitidis.

Therapy consisted of 25 million units of sodium penicillin in the first eight hours and 200 million units of potassium penicillin in the first 48 hours by the intravenous route. Sensitivity studies were carried out and the organisms were found to be resistant to penicillin, moderately sensitive to streptomycin and highly sensitive to chloramphenicol, aureomycin and Terramycin. The patient was given 250 mg. of Terramycin intravenously every four hours for four days. Then the antibiotic was given by mouth until Feb. 25 when therapy was discontinued. Sulfadiazine and sulfisomidine, 2.5 gm. each, were given every eight hours by clysis for eight times, and then 0.5 gm. each orally every four hours for four days. The evening of admission, gastric suction was applied and was continued for one day; "coffee ground" material was removed.

Improvement was pronounced, particularly in the first 48 hours. The first evening there were three generalized convulsions; after that, none. The temperature decreased from 104.6° to 98.6° F. eight hours after admission. It then varied from 98.6° to 100.8° F. for seven days and after that was normal. Data on laboratory examinations of cerebrospinal fluid and blood are given in Table 3.

Reports on electroencephalograms made during the illness were as follows: Feb. 11, diffusely abnormal; Feb. 20, mild diffusely abnormal; Feb. 27, normal.

Antibiotic therapy was discontinued Feb. 25 and the patient was discharged, well, March 6, 28 days after admission.

## DISCUSSION

In the three cases of meningococcus meningitis presented, the organisms were resistant to penicillin. If it had been decided that penicillin was the drug of choice, since Neisseria meningitidis usually is so sensitive to it, and no other agent had been used, the end result might have been fatal. Fortunately, two antibiotics were used at the beginning of therapy with the thought in mind that if the organisms were not sensitive to one antibiotic they might be to the other. With the widespread use of antibiotics today for minor illnesses, it seems logical, when meningitis is diagnosed, to use two or more in the initial therapy until sensitivity studies are done.

## SUMMARY

Three cases of meningococcus meningitis are reported in which the infecting organisms were resistant to penicillin, as sensitivity studies determined. Fortunately, other antibiotics were used with penicillin at the outset of therapy.

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